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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,519	05/01/2002	Audrey Goddard	P3230R1C001-168	8149

30313 7590 01/11/2007

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/063,519	GODDARD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 16 October 2006 has been entered.

2. Claims 1–5 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

5. The objection to the disclosure as not complying with the sequence rules is withdrawn in view of the sequence listing filed 10/16/06 and applicants' statement that the previously submitted computer readable form and the instant paper copy of the sequence listing are identical and do not contain new matter field 10/16/06.

6. The Objection to the title as not being descriptive of the claimed invention is withdrawn in view of the newly submitted title filed 10/16/2006.

Rejections Maintained

Claim Rejections - 35 USC §§ 101, 112

7. Claims 1–5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Applicants point out that in other applications filed by Applicants that rely on data from the exact same disclosure, Example 18, and in which the Applicants have submitted substantially the same references in support of their asserted utility, the PTO has concluded that: "[b]ased on the totality of evidence of record, one of skill in the art would find it more likely than not that an increase in message as measured by RT-PCR would be predictive of an increase in protein expression levels absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1864, also supports a conclusion of differential expression of PRO1864 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1864 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant." Applicants submit that the Examiners Reasons for Allowance in pending Application No. 10/063,529, No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583 conclude that the data presented in Example 18 demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides and support a conclusion of differential expression of the PRO polypeptides, which makes the claimed PRO polypeptides and antibodies that bind the

PRO polypeptides useful for diagnostic purposes. Applicants request that the Examiner recognize the utility of the claimed invention, as was done in the other applications referenced above. Applicants' arguments have been fully considered but they are not persuasive. Suffice it to say that each case must be decided on its own merits based on the evidence of record. Additionally, Applicant is advised that an examiner's conclusions in another pending application based on it's own merits are not representative, nor reflective of any particular conclusion by the PTO.

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1864 gene is more highly expressed in melanoma compared to normal skin tissue, and is therefore useful as a diagnostic tool for melanoma; that this utility is substantial; that this asserted utility is credible. Applicants remind the Examiner that Applicants enjoy a presumption that their assertions are true; that the Examiner must approach Applicants' assertion of utility as being sufficient to satisfy the utility requirement; that with respect to the use of the PRO1864 nucleic acid to distinguish tumor from normal tissue, the Examiner must accept this assertion as true "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility;" that therefore, the question is whether the PTO has established that there is a reason to doubt the objective truth of Applicants' assertion that using standard RT-PCR procedures to examine the expression of the PRO1864 mRNA in pooled normal skin samples and pooled melanoma samples, Applicants discovered that PRO1864 mRNA is differentially expressed between normal and tumor tissue such that it can be used as a diagnostic

tool; that the PTO has set a heightened requirement for Applicants to demonstrate utility based on the disclosed differential expression; that the PTO fails to support this heightened requirement with any evidence whatsoever; that the PTO provides no evidence or findings of facts to suggest that one skilled in the art would doubt Applicants' disclosed differential expression; that based on the complete failure to present any evidence whatsoever to bring into question Applicants' disclosed differential expression, Applicants submit that the PTO's heightened requirements for evidence are improper and insufficient to overcome Applicants' presumption of utility. Applicants' arguments have been fully considered but they are not persuasive. The examiner considers these arguments somewhat misleading because applicants have never been asked to prove the diagnostic utility of the PRO1864 polynucleotide, polypeptide, and antibodies thereto. Rather, the facts to be established are is the reported change in PRO1864 mRNA expression tumor-dependent, and if so, is there a corresponding change in the level of the PRO1864 polypeptide. Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Applicants have not provided any testing of the expression of the PRO1864 polypeptide. In the absence of any information on the role, activity or expression of the PRO1864 polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if the reported

change in PRO1864 transcripts is tumor-dependent or tumor-independent and would not know if or how PRO1864 polypeptide expression would change in cancer. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist. The specification does not establish if the disclosed change in PRO1864 mRNA expression is one of those cases where there is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO1864 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO1864 polypeptide, the specification does not provide some immediate benefit to the public for the PRO1864 polypeptide and claimed antibodies thereto.

Applicants argue that the results of Example 18 reflect at least a two-fold difference between normal and tumor samples; that since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant, as is the baseline level of expression; that contrary to the Examiner's position that the statements in Mr. Grimaldi's Declaration are "conclusory and unsupported," Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue; that Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue.

Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned;" that in addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the PTO's position. The first Grimaldi declaration (Exhibit 1, 5/2/2005) has been considered. However, the MPEP makes clear, "factual evidence is preferable to opinion testimony...." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight. In the present case, the declaration does not provide anything specific concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. It is unknown what level of difference is being reported or how many

samples were tested. Given the paucity of information regarding PRO1864 mRNA expression and the complete lack of data concerning PRO1864 polypeptide expression, Hu is evidence that a skilled artisan would consider the precise level of PRO1864 gene expression as relevant.

With respect to the Hu reference, Applicants maintain that this reference does not contradict Applicants' position because it focuses on the causative role of polypeptides in cancer. Applicants reiterate that, whether or not the PRO1864 polypeptide is the causative agent of cancer, the claimed polypeptides are useful as diagnostic agents. In addition, Applicants argue that Hu cannot support the Examiner's dismissal of the first Grimaldi Declaration because it is silent regarding the use of differentially expressed genes as diagnostic tools in general, and the reliability of pooled samples in particular. In particular, applicants argue that Hu says nothing about whether or not differential expression in pooled samples is susceptible to disease-independent differences between samples and the Examiner has not offered any arguments or evidence to counter Grimaldi's statements. Therefore, applicants argue that Hu does not provide a basis for doubting Applicants' differential expression data. As such, applicants argue that there is no evidence that one skilled in the art would question whether the differential expression of PRO1864 mRNA in pooled samples was disease-dependent or disease-independent. Applicants' arguments have been fully considered but they are not persuasive. Although the declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal

and of tumor tissues, this statement is in contrast to the specification's teachings, which discloses:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Page 140, paragraph 0530.

The declaration does not provide anything specific concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. It is unknown what level of difference is being reported or how many samples were tested. Hu concludes that even when expression changes as small as 2-fold are statistically significant, it is not always clear if they are biologically meaningful. These small changes in expression may reflect genes whose role in cancer may not involve large changes in expression or genes whose modest changes in expression may be unrelated to the disease. A gene whose change in expression is unrelated to the disease cannot be used as a marker for the disease.

Furthermore, Applicants argue that Hu is not relevant to the present application, which does not rely on microarray data. In this regard, Applicants rely on Kuo (Exhibit 1, 5/1/2006). Applicant finds no basis in the Kuo reference to question whether or not the detected differences in mRNA levels were CpG-ODN dependent and maintains that this issue is not pertinent to the utility of the claimed antibodies. Applicants' arguments have been fully considered but they are not persuasive. From the evidence provided it cannot be ascertained if Kuo's microarray data was consistent or inconsistent with Kuo's RT-PCR data. Therefore, there is no basis for asserting that "microarrays are

simply not relevant to Applicants' RT-PCR data." Kuo's poor correlation between microarray and proteomic expression profiles does not speak to changes in mRNA attributable to disease-independent differences between samples. Regarding Hu, a gene whose change in expression is unrelated to the disease cannot be used as a marker for the disease because the change is unrelated to the disease. Further, unlike the present application, Kuo et al actually analyzed mRNA and protein levels and performed functional assays. The instant application merely measures mRNA and presumes that PRO1864 polypeptide levels will track with the changes in PRO1864 mRNA, without providing any evidence of how PRO1864 polypeptide levels change in melanomas compared to normal skin and does not disclose any biological activity or function for the PRO1864 polypeptide. The specification does not provide any evidence that the PRO1864 polypeptide can be used in a diagnostic or therapeutic setting, what information the PRO1864 polypeptide expression provides the clinician, such as the status of the cancer, or the direction in which therapy should proceed.

Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1864 mRNA between melanoma compared to normal skin tissue and that the data in Example 18 are reliable. Applicants argue that the PTO presents no evidence to support the assertions that the use of pooled samples obscures the degree of variation between samples, making the disclosed results less useful, accurate and informative than if results from individual samples had been provided. Applicants argue that thus, the PTO uses conclusory and unsupported arguments as the basis for dismissing the

declaration of an expert; that as such, the PTO's position is inconsistent with the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered" and also is inconsistent with the requirement of the PTO to support its assertions of fact; that absent supporting evidence, it is inappropriate for the PTO to dismiss Applicants' arguments and Mr. Grimaldi's opinion regarding pooled samples simply because the PTO wishes to take a contrarian position on the use of pooled samples in diagnostics. Applicants argue that in particular, use of a pooled sample is a more accurate indication of whether an observed change is tumor-dependent than use of individual samples because the observed extent of differential mRNA levels between tumor tissue and normal tissue is normalized to reflect the typical degree of variation within the pool; that as previously pointed out, should there be a particular sample in the pool which exhibits an atypical degree of variation between tumor tissue and normal tissue, the effects of that sample on the observed degree of variation are mitigated by the other members of the pool; that accordingly, the observation of differential mRNA expression in tumor tissue compared to normal tissue using pooled samples is a reliable indication that such differential expression is in fact disease dependent. Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1864 mRNA in melanoma compared to normal skin tissue. Applicants' arguments have been fully considered but they are not persuasive.

Pooled samples eliminate the effect of variation on applicants' conclusion regarding differential PRO1864 mRNA expression. However, pooled samples do not eliminate the variation itself. Without knowledge of the degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. The examiner believes that he has adequately supported his arguments.

Applicants continue to maintain that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; that given Applicants' evidence of differential expression of the mRNA for the PRO1864 polypeptide in melanoma, it is likely that the PRO1864 polypeptide is also differentially expressed; and antibodies which bind to proteins differentially expressed in certain tumors have utility as diagnostic tools. In support, Applicant argues the teachings of Lian, Fessler and Ornoft, which according to Applicant do not contradict Applicants' position that, in general, a change in mRNA level corresponds to a change in the level of polypeptide. Applicants arguments have been fully considered but are not found persuasive. Contrary to Applicants' arguments the facts to be established are: (i) is the reported change in PRO1864 transcripts tumor-dependent or tumor-independent and, if the reported change is tumor-dependent, is there a corresponding change in PRO1864 polypeptide expression. The specification does not establish if the disclosed change in PRO1864 mRNA expression is one of those cases where there is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Applicants have not provided any testing of PRO1864 polypeptide expression. Therefore, there is no reason for a

skilled artisan to be reasonably convinced that the PRO1864 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO1864 polypeptide, the specification does not provide some immediate benefit to the public for the PRO1864 polypeptide and claimed antibodies thereto. The correlation between the disclosed change in PRO1864 mRNA and a change in PRO1864 polypeptide expression is unknown and is not disclosed. Further, the fact that there may be a commonly understood general correlation that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist as evidenced by the record, i.e., Lian reference.

Applicants maintain that Applicants need only show that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true. For the reasons previously submitted, Applicants maintain that one skilled in the art would believe that, in view of the differential expression of the PRO1864 mRNA, it is more likely than not that the PRO1864 polypeptide is also differentially expressed. This has been fully considered but is not found persuasive. A probable utility does not establish a practical utility, which is established by actual testing or where the utility can be "foretold with certainty." *Bindra v. Kelly*, 206 USPQ 570, 575 (Bd. Pat. Inter. 1979) (Reduction to practice was not established for an intermediate useful in the preparation of a second intermediate with a known utility in the preparation of a pharmaceutical. The record established there was a high degree of

probability of a successful preparation because one skilled in the art may have been motivated, in the sense of 35 U.S.C. 103, to prepare the second intermediate from the first intermediate. However, a strong probability of utility is not sufficient to establish practical utility.). Practical utility is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner, which provides some immediate benefit to the public.

Regarding the numerous levels of control of protein synthesis, Applicants continue to maintain that, while transcription initiation is not the only point at which gene expression is regulated, it is the predominant mechanism for regulating gene expression. Similarly, with respect to Molecular Biology of the Cell (3rd ed.), Genes VI, and the Meric reference, Applicants continue to maintain that transcription initiation is the predominant point at which gene expression is regulated. Applicants incorporate by reference the previous arguments regarding these references, and will not repeat them here. In response, the examiner incorporates by reference his previous arguments, and will not repeat them here.

Applicants submit herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 1). Applicants argue that that applicants submit the opinion of yet another expert in the field that changes in mRNA level for a particular protein in a given tissue generally lead to a corresponding change in the level of the encoded protein; that Dr. Scott's opinion is supported by Dr. Scott's extensive experience in the field, as well as the fact that an entire industry has developed around technology to assess differential mRNA expression. Applicants argue that, as stated previously, there would

be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels. Applicants' arguments have been fully considered but they are not persuasive. The declaration under 37 CFR 1.132 filed by Randy Scott is insufficient to overcome the rejection of claims 1–5. Dr. Scott bases his conclusions on microarray data, which applicants have disparaged as inaccurate and unreliable. Further, Dr. Scott does not provide any data concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in any type of tissue sample. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to first and second Polakis declarations and because there are some exceptions on an individual gene basis, according to the Scott declaration. Neither the specification nor any of applicants' arguments or other evidence establish if the disclosed change in PRO1864 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO1864 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO1864 polypeptide, the specification does not provide some immediate benefit to the public for the PRO1864 polypeptide.

Applicants argue that the second declaration of Dr. Polakis has provided the facts to enable the PTO to draw independent conclusions. Applicants argue that the case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines, which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Applicant argues that the two additional expert Declarations submitted herewith in addition to the declarations and over 115 references already of record, support Applicants' asserted utility, either directly or indirectly; that this evidence supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. Applicants acknowledge that the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. Therefore, applicants argue that the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." Applicants' arguments have been fully

considered but they are not persuasive. The second Polakis declaration has been considered. Like the first Polakis declaration, the second Polakis declaration does not provide any data concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to Dr. Polakis. The MPEP makes clear, "factual evidence is preferable to opinion testimony ... ." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP §716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things:

(1) The nature of the fact sought to be established.

(2) The strength of any opposing evidence.

(3) The interest of the expert in the outcome of the case.

(4) The presence or absence of factual support for the expert's opinion.

Unless an "expert" states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight.

The facts to be established are whether or not the disclosed change in PRO1864 transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO1864 transcripts and a corresponding change in PRO1864 polypeptides levels. The declarations do not provide any data concerning PRO1864 mRNA expression, PRO1864 polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. According to the first Polakis declaration:

> The purpose of this research is to identify proteins that are abundantly expressed on certain tumor cells and that are either (i) not expressed, or (ii) expressed at lower levels, on corresponding normal cells. Paragraph 3.
>
> ... we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal cells. Paragraph 4.

The corresponding paragraphs from the second Polakis declaration say essentially the same thing except that instead of stating "significantly higher levels than in corresponding normal cells" the second Polakis declaration at paragraph 4 states "significantly higher levels in normal human tissue." Both the first and second Polakis declarations indicate that the data was generated using microarray analysis, which applicants' have disparaged as inaccurate and unreliable. There is no evidence of record that either the PRO1864 mRNA or the PRO1864 polypeptide is abundantly expressed in either tumor tissue or normal tissue. Given the paucity of information regarding PRO1864 mRNA expression in tumors and the evidence in the art that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art

would not know if the change in PRO1864 mRNA expression was disease-dependent or disease-independent, would not know if or how PRO1864 polypeptide expression would change in tumors, and would have a reasonable, legitimate basis to doubt the utility of the PRO1864 polypeptide. Even if the examiner were to assume that the disclosed change in PRO1864 transcripts could reasonably be correlated with an assumed change in PRO1864 polypeptide expression, it still could not be ascertained if the assumed change in PRO1864 polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO1864 transcripts is disease-dependent or disease-independent. Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO1864 polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to first Polakis declaration, and 10% of the cases examined do not show a correlation, according to second Polakis declaration. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1864 transcripts and PRO1864 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to the Polakis declarations.

Applicants argue that the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed antibodies - specifically, direct evidence of differential expression of PRO1864 polypeptide in tumor

and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts. Applicants argue that the PTO implies the following argument: (1) the evidence of record demonstrates that there are exceptions to the general rule that increased mRNA levels correspond to increased levels of the encoded polypeptide; (2) because such exceptions exist, it is mandatory that specific data of differential PRO1864 polypeptide expression in normal skin tissue as compared to melanoma; and (3) since such is not disclosed, the claimed antibodies that bind the PRO1864 polypeptide have no substantial utility. Applicants argue that adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto; that thus, the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility; that this heightened utility requirement is inconsistent with the Utility Guidelines and the courts; that there is no requirement that utility be dispositively proven; that the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt;" that nor is the requirement that only direct evidence of utility is sufficient to establish utility; that instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101; that furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility; that instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility; that the indirect evidence need not absolutely prove the asserted utility; that all that is required is

that the tests be reasonably indicative of the asserted utility; that in other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a reasonable probability, that the novel compound will possess the asserted utility; that the PTO appears to consider the above guidance from the courts inapplicable to the present situation because in those cases the claimed compound had been tested, and, in the present test, the polypeptides to which the claimed antibodies specifically bind have not been tested; that however, the PTO's position fails to recognize the issue in question for the above cases; that the issue in question was whether or not Appellants' evidence (in vitro or animal testing of compound), which was different in nature from the asserted utility (therapeutic use of compound), was sufficient to fulfill the requirements of 35 U.S.C. §101 when there was a reasonable link between Appellants' evidence and the asserted utility; that in the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide); that insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. §101 as provided by the guidance of the Utility Guidelines and the courts; Applicants maintain that, in general, changes in mRNA levels correlate with changes in the levels of the encoded polypeptides; that accordingly, applicants maintain that it is more likely than not that the PRO1864 polypeptide is differentially expressed in melanoma. Applicants' arguments have been fully considered but they are not persuasive. It is the examiner's position that Applicants

should provide substantial evidence of a diagnostic utility unless one of skill in art would accept such utility as obviously correct. There is no indication that a skilled artisan would accept without question that the reported change in PRO1864 transcripts is tumor-dependent or that the PRO1864 polypeptide is differentially expressed in tumor tissue as compared to normal tissue in a manner consistent with the reported change in PRO1864 transcripts. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provides any specific data disclosing if or how PRO1864 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO1864 transcripts and PRO1864 polypeptide expression to argue that it is more likely than not that a change in PRO1864 transcripts is correlated with an assumed change in PRO1864 polypeptide expression. Without any evidence of the expression of PRO1864 in tumor tissue this argument is of no avail to Applicants. Applicants' arguments, exhibits and declarations only show that it is not implausible that invention will work for its intended purpose. A probable utility does not establish a practical utility, which is established by actual testing or where the utility can be "foretold with certainty." *Bindra v. Kelly*, 206 USPQ 570, 575 (Bd. Pat. Inter. 1979). However, a strong probability of utility is not sufficient to establish practical utility.). Practical utility is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner, which provides some immediate benefit to the public. In view of the countervailing evidence, Applicants' arguments, exhibits and declarations are

insufficient to meet the utility requirement because they are insubstantial evidence that expression of the PRO1864 polypeptide changes in a manner that corresponds to the reported change in PRO1864 transcripts.

Applicants submit that the evidence of differential expression of the PRO1864 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides. Applicants argue that, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1864 gene and polypeptide with a specific disease; that the asserted utility for the claimed antibodies as diagnostic tools for cancer, particularly melanoma, is a specific utility — it is not a general utility that would apply to the broad class of polypeptides. Applicants' arguments have been fully considered but they are not persuasive. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility.

8. Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a

matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

New Grounds of Rejections

Priority

Applicant claims priority to three previous applications. Priority is granted to PCT/US00/23328, filed 24 August 2000, as the disclosure of '328 is identical to the instant disclosure. However, priority is not granted to 60/170,262 since this application does not disclose the quantitative PCR analysis measuring the PRO1864 mRNA (Example 18) upon which applicant relies for utility of the instantly claimed polypeptide and antibodies thereto. Therefore, the filing date for the purpose of art rejections is deemed to be 24 August 2000. Applicant is reminded that benefit to a prior-filed application requires written description and enablement under the first paragraph of 35 U.S.C. 112.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Tang et al (WO 01/53312, priority to 1/21/2000).

Tang et al teach a polypeptide (i.e., SEQ ID NO:6646) that is identical to the polypeptide of SEQ ID NO:14 (see attached alignment; Exhibit A) and antibodies to the polypeptide, including monoclonal and humanized antibodies as well as antibody fragments and labels (pp. 1-104, 291, 535; particularly pp. 74-84, 291 and 535).

Thus, Tang et al anticipates the claims.

Conclusion

11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

Exhibit A

RESULT 624
AAM41715
ID AAM41715 standard; protein; 238 AA.
XX
AC AAM41715;
XX
DT 22-OCT-2001 (first entry)
XX
DE Human polypeptide SEQ ID NO 6646.
XX
KW Human; nootropic; immunosuppressant; cytostatic; gene therapy; cancer;
KW peripheral nervous system; neuropathy; central nervous system; CNS;
KW Alzheimer's; Parkinson's disease; Huntington's disease; haemostatic;
KW amyotrophic lateral sclerosis; Shy-Drager Syndrome; chemotactic;
KW chemokinetic; thrombolytic; drug screening; arthritis; inflammation;
KW leukaemia.
XX
OS Homo sapiens.
XX
PN WO200153312-A1.
XX
PD 26-JUL-2001.
XX
PF 26-DEC-2000; 2000WO-US034263.
XX
PR 23-DEC-1999; 99US-00471275.
PR 21-JAN-2000; 2000US-00488725.
PR 25-APR-2000; 2000US-00552317.
PR 20-JUN-2000; 2000US-00598042.
PR 19-JUL-2000; 2000US-00620312.
PR 03-AUG-2000; 2000US-00653450.
PR 14-SEP-2000; 2000US-00662191.
PR 19-OCT-2000; 2000US-00693036.
PR 29-NOV-2000; 2000US-00727344.
XX
PA (HYSE-) HYSEQ INC.
XX
PI Tang YT, Liu C, Asundi V, Chen R, Ma Y, Qian XB, Ren F, Wang D;
PI Wang J, Wang Z, Wehrman T, Xu C, Xue AJ, Yang Y, Zhang J, Zhao QA;
PI Zhou P, Goodrich R, Drmanac RT;
XX
DR WPI; 2001-442253/47.
DR N-PSDB; AAI60871.
XX
PT Novel nucleic acids and polypeptides, useful for treating disorders such
PT as central nervous system injuries.
XX
PS Example 2; SEQ ID NO 6646; 10078pp; English.
XX
CC The invention relates to human nucleic acids (AAI57798-AAI61369) and the
CC encoded polypeptides (AAM38642-AAM42213) with nootropic,
CC immunosuppressant and cytostatic activity. The polynucleotides are useful
CC in gene therapy. A composition containing a polypeptide or polynucleotide
CC of the invention may be used to treat diseases of the peripheral nervous
CC system, such as peripheral nervous injuries, peripheral neuropathy and
CC localised neuropathies and central nervous system diseases, such as
CC Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic

CC lateral sclerosis, and Shy-Drager Syndrome. Other uses include the
CC utilisation of the activities such as: Immune system suppression,
CC Activin/inhibin activity, chemotactic/chemokinetic activity, haemostatic
CC and thrombolytic activity, cancer diagnosis and therapy, drug screening,
CC assays for receptor activity, arthritis and inflammation, leukaemias and
CC C.N.S disorders. Note: The sequence data for this patent did not form
CC part of the printed specification
XX
SQ Sequence 238 AA;

Query Match 100.0%; Score 1195; DB 4; Length 238;
Best Local Similarity 100.0%; Pred. No. 1.7e-131;
Matches 234; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 MNHLPEDMENALTGSQSSHASLRNIHSINPTQLMARIESYEGREKKGISDVRRTFCLFVT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          5 MNHLPEDMENALTGSQSSHASLRNIHSINPTQLMARIESYEGREKKGISDVRRTFCLFVT 64

Qy         61 FDLLFVTLLWIIELNVNGGIENTLEKEVMQYDYYSSYFDIFLLAVFRFKVLILAYAVCRL 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         65 FDLLFVTLLWIIELNVNGGIENTLEKEVMQYDYYSSYFDIFLLAVFRFKVLILAYAVCRL 124

Qy        121 RHWWAIALTTAVTSAFLLAKVILSKLFSQGAFGYVLPIISFILAWIETWFLDFKVLPQEA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        125 RHWWAIALTTAVTSAFLLAKVILSKLFSQGAFGYVLPIISFILAWIETWFLDFKVLPQEA 184

Qy        181 EEENRLLIVQDASERAALIPGGLSDGQFYSPPESEAGSEEAEEKQDSEKPLLEL 234
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        185 EEENRLLIVQDASERAALIPGGLSDGQFYSPPESEAGSEEAEEKQDSEKPLLEL 238
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